

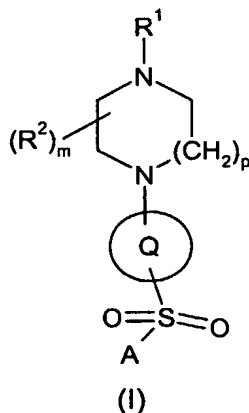
10/509077

NOVEL COMPOUNDS

This invention relates to novel quinoline and aza indole compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081 discloses a series of aryl sulphonamide compounds that are said to be 5-HT₆ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. GB-2341549, WO 99/47516 and WO 99/65906 all disclose a series of indole derivatives that are claimed to have 5-HT₆ receptor affinity. JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements. WO 01/83456 (Yamanouchi Pharmaceutical Co. Ltd) describes a series of bicyclic or tricyclic fused heteroaryl compounds with phosphatidylinositol 3-kinase activity. WO 00/42026 (Novo Nordisk) describes a series of quinoline and quinoxaline compounds for use as GLP-1 agonists. JP 08003144 (Chugai Pharmaceutical Co. Ltd.) describes a series of quinazoline and quinoline derivatives as potassium channel openers. WO 97/03069 (Glaxo Group Limited) and WO 96/09294 (The Wellcome Foundation Limited) both describe a series of substituted quinolines and quinazolines as protein tyrosine kinase inhibitors.

A structurally novel class of compounds has now been found which also possess affinity for the 5-HT₆ receptor. The present invention therefore provides, in a first aspect, a compound of formula (I), or a pharmaceutically acceptable salt thereof:



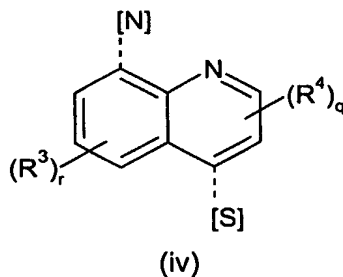
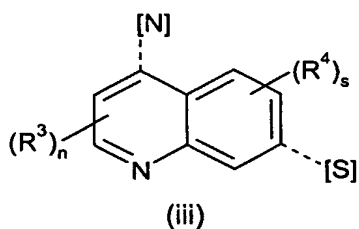
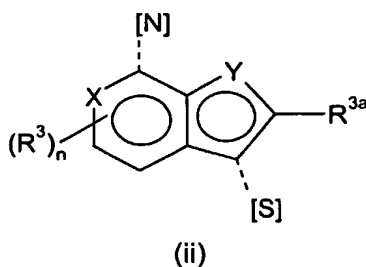
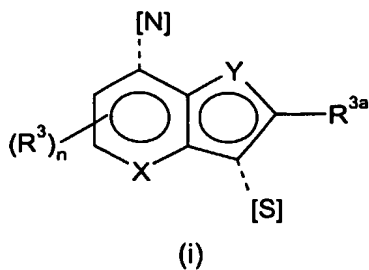
wherein

R¹ and R² independently represent hydrogen or C₁₋₆ alkyl or R¹ is linked to R² to form a group (CH₂)₂, (CH₂)₃ or (CH₂)₄;

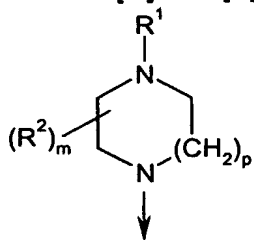
p represents 1 or 2;

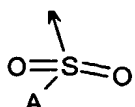
m represents an integer from 1 to 4, when m is an integer greater than 1, two R² groups may instead be linked to form a group CH₂, (CH₂)₂ or (CH₂)₃;

Q represents a group of formula (i), (ii), (iii) or (iv):



wherein [N] and [S] represent the attachment points for the groups



and  respectively;

one of X and Y represents $-N=$ and the other represents $-N(R^5)-$;

- 15 R^3 and R^4 independently represent hydrogen, halogen, cyano, $-CF_3$, $-OCF_3$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^6R^7$;
 R^{3a} and R^5 independently represent hydrogen or C_{1-6} alkyl;

R⁶ and R⁷ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

n and q independently represent 1 or 2;

5 r and s independently represent an integer from 1 to 3;

A represents a group -Ar¹ or -Ar²Ar³;

Ar¹, Ar² and Ar³ independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of

10 halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁₋₆ alkoxy, arylC₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxyC₁₋₆ alkyl, C₃₋₇ cycloalkylC₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆ alkylsulfonylC₁₋₆ alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₆ alkyl, C₁₋₆ alkylsulfonamido, C₁₋₆ alkylamido, 15 C₁₋₆ alkylsulfonamidoC₁₋₆ alkyl, C₁₋₆ alkylamidoC₁₋₆ alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC₁₋₆ alkyl, arylcarboxamidoC₁₋₆ alkyl, aroyl, aroylC₁₋₆ alkyl, arylC₁₋₆ alkanoyl, or a group CONR⁸R⁹ or SO₂NR⁸R⁹, wherein R⁸ and R⁹ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; 20 or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight branched and the groups alkoxy and alkanoyl shall be interpreted similarly. 25 moieties are more preferably C₁₋₄ alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

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The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, 35 isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinoliny, isoquinoliny, quinazolinyl, quinoxaliny, cinnoliny, naphthyridiny, indolyl, indazolyl, pyrrolopyridiny, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, 40 benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

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For compounds of formula (I) wherein Q represents a group of formula (i):

Preferably, R^1 represents hydrogen or methyl, more preferably hydrogen.

Preferably R^2 represents hydrogen or methyl.

Preferably R^3 represents hydrogen, methyl or halogen, more preferably hydrogen.

10

Preferably R^{3a} and R^5 independently represent hydrogen or methyl.

Preferably m, n and p each represent 1.

When A represents a group $-Ar^1$, Ar^1 preferably represents optionally substituted phenyl or pyridyl, more preferably phenyl optionally substituted with halogen, cyano, trifluoromethyl or trifluoromethoxy. Particularly preferred Ar^1 is phenyl optionally

15

substituted with halogen (such as 2-fluorine).

When A represents a group $-Ar^2-Ar^3$, Ar^2 and Ar^3 preferably both independently represent phenyl or monocyclic heteroaryl group as defined above.

Preferably A represents a group $-Ar^1$.

20

For compounds of formula (I) wherein Q represents a group of formula (ii):

Preferably, R^1 represents hydrogen or methyl, more preferably hydrogen.

Preferably R^2 represents hydrogen.

Preferably R^3 represents hydrogen, methyl or halogen, more preferably hydrogen.

Preferably X represents $-N=$.

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Preferably Y represents $-N(R^5)-$.

Preferably R^{3a} and R^5 independently represent hydrogen or methyl, more preferably hydrogen.

Preferably m, n and p each represent 1.

When A represents a group $-Ar^1$, Ar^1 preferably represents optionally substituted phenyl or pyridyl, more preferably phenyl optionally substituted with halogen, cyano, trifluoromethyl or trifluoromethoxy. Particularly preferred Ar^1 is phenyl optionally substituted with halogen (such as 2-fluorine and 3-fluorine).

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When A represents a group $-Ar^2-Ar^3$, Ar^2 and Ar^3 preferably both independently represent phenyl or monocyclic heteroaryl group as defined above.

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Preferably A represents a group $-Ar^1$.

For compounds of formula (I) wherein Q represents a group of formula (iii):

Preferably, R^1 represents hydrogen or methyl, more preferably hydrogen.

Preferably R^2 represents hydrogen.

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Preferably R^3 represents hydrogen, methyl or halogen, more preferably hydrogen or methyl.

Preferably R^4 represents hydrogen or halogen, more preferably hydrogen.

Preferably m, n, p and s each represent 1.

When A represents a group $-\text{Ar}^1$, Ar^1 preferably represents optionally substituted phenyl or pyridyl, more preferably phenyl optionally substituted with halogen, cyano, trifluoromethyl or trifluoromethoxy. Particularly preferred Ar^1 is unsubstituted phenyl.

- 5 When A represents a group $-\text{Ar}^2-\text{Ar}^3$, Ar^2 and Ar^3 preferably both independently represent phenyl or monocyclic heteroaryl group as defined above; Preferably A represents a group $-\text{Ar}^1$.

For compounds of formula (I) wherein Q represents a group of formula (iv):

- 10 Preferably, R^1 represents hydrogen or methyl, more preferably hydrogen.

Preferably, R^2 represents hydrogen.

Preferably, R^3 represents hydrogen or a halogen atom.

Preferably, R^4 represents hydrogen or methyl (particularly 2-methyl).

Preferably, m, p, q and r all represent 1.

- 15 When A represents $-\text{Ar}^2\text{Ar}^3$, Ar^3 is preferably linked to Ar^2 via a carbon atom of Ar^3 , and preferably Ar^2 and Ar^3 independently represent phenyl or a monocyclic heteroaryl group as defined above.

Preferably, A represents $-\text{Ar}^1$.

- 20 Preferably, $-\text{Ar}^1$ is phenyl or pyridyl optionally substituted by one or more halogen atoms or cyano, trifluoromethoxy or trifluoromethyl groups, more preferably unsubstituted phenyl, 2-fluorophenyl, 3-fluorophenyl or 3-chlorophenyl.

Preferred compounds according to the invention include examples E1-E16 as shown below, or a pharmaceutically acceptable salt thereof.

25

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

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The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

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Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these

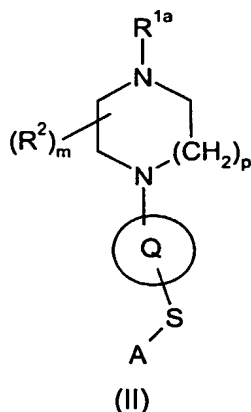
stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

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The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

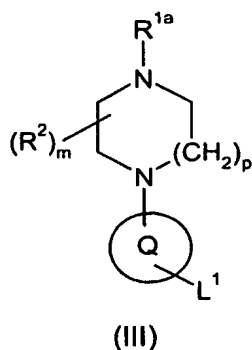
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- (a) oxidation of a compound of formula (II)



wherein R^{1a} is as defined for R^1 or an *N*-protecting group and Q, R^2 , m, p and A are as defined above, and thereafter as necessary removing an R^{1a} *N*-protecting group; or

- (b) preparing a compound of formula (I) wherein Q represents a group of formula (iii) or (iv) which comprises reacting a compound of formula (III)



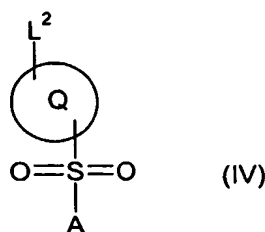
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wherein R^{1a} is as defined for R^1 or an *N*-protecting group, R^2 , m and p are as defined above and L^1 is a suitable leaving group such as iodo or trifluoromethanesulfonyloxy;

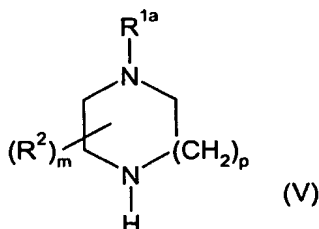
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with a compound of formula A-SO₂H, (or A-SH followed by a subsequent oxidation step) wherein A is as defined above and thereafter as necessary removing an R^{1a} *N*-protecting group; or

- (c) preparing a compound of formula (I) wherein Q represents a group of formula (iii) or (iv) which comprises reacting a compound of formula (IV)



- 5 wherein A is as defined above and L^2 represents a leaving group, such as a halogen atom,
with a compound of formula (V)



- 10 wherein R^{1a} is as defined for R^1 or an *N*-protecting group such as *tert*-butyloxycarbonyl (t-Boc), R^2 , m and p are as defined above, followed by subsequent deprotection if necessary; or

- 15 (d) deprotecting a compound of formula (I) which is protected; and thereafter optionally

- (e) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

- 20 The *N*-protecting group used may be any conventional group e.g. *t*-butyloxycarbonyl (Boc) or benzyloxycarbonyl.

- 25 Process (a) typically comprises the use of an oxidant such as a peracid (e.g. 3-chloroperbenzoic acid or peracetic acid) or potassium monopersulfate, in a suitable solvent such as dichloromethane or aqueous methanol.

- 30 Process (b) wherein a compound of formula (III) is reacted with a compound of formula $A-SO_2H$ typically comprises use of basic conditions and may be most conveniently carried out by using a suitable salt of the compound $A-SO_2H$ (e.g. the sodium salt) in an appropriate solvent such as *N,N*-dimethylformamide, in the presence of a transition metal salt such as copper (I) iodide.

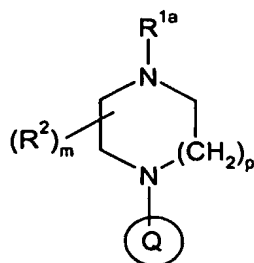
Process (b) wherein a compound of formula (III) is reacted with a compound of formula A-SH typically comprises use of basic conditions e.g. by using a suitable salt of the compound A-SH (e.g. the sodium salt) in an appropriate solvent such as *N,N*-dimethylformamide, in the presence of a suitable metal salt such as copper (I) iodide,
5 followed by use of a suitable oxidant such as 3-chloroperbenzoic acid, peracetic acid or potassium monopersulfate.

Process (c) typically comprises the use of a palladium catalyst, eg. palladium acetate in the presence of a suitable ligand, eg. BINAP and a suitable base, eg. caesium carbonate
10 in a suitable solvent, eg. dioxane.

In processes (a), (b), (c) and (d), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl
15 (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-COCF₃)
20 which may be removed by base catalysed hydrolysis, or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis (e.g. with trifluoroacetic acid). A further amine protecting group is a benzyl group which may be removed using standard methods for *N*-dealkylation (e.g. with ethyl chloroformate
25 under basic conditions followed by treatment with methanol).

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, *N*-dealkylation of a
30 compound of formula (I) wherein R¹ represents an alkyl group to give a compound of formula (I) wherein R¹ represents hydrogen. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion. It will also be appreciated that attempted conversion of optionally protected compounds of formula (I) wherein R⁵
35 represents hydrogen into other optionally protected compounds of formula (I) wherein R⁵ represents C₁₋₆alkyl using conventional alkylation methods may give rise to mixtures containing varying amounts of the corresponding regioisomers. Such mixtures may be separated by conventional means, for example using flash chromatography.

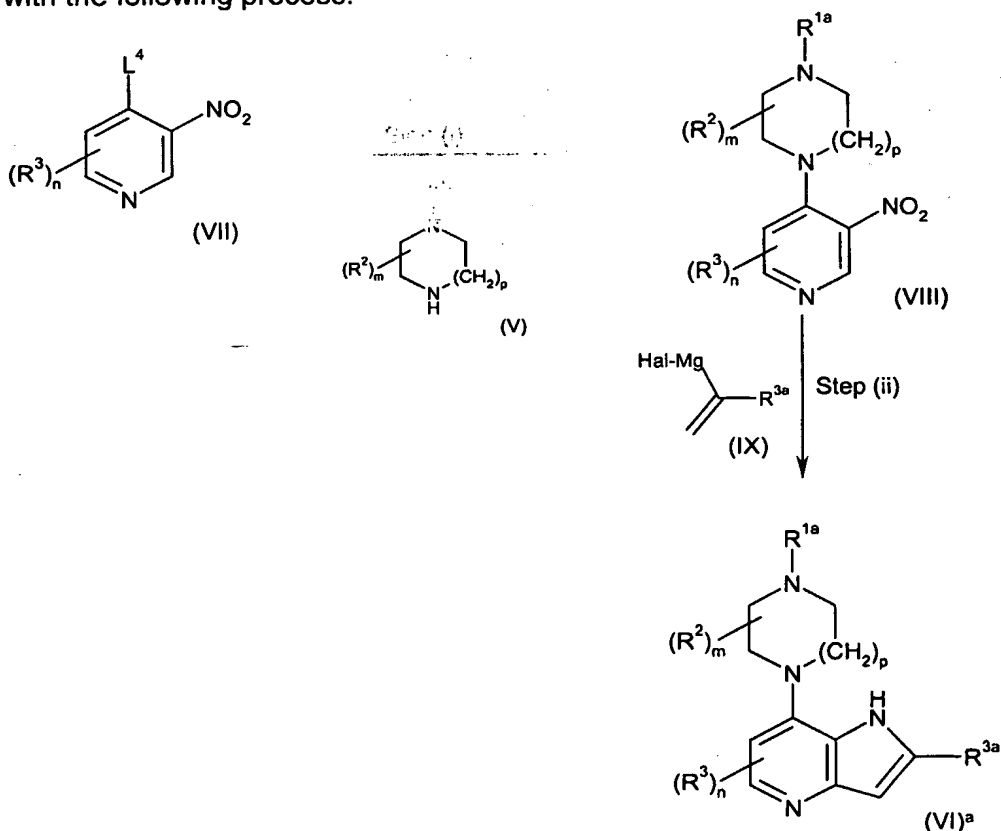
40 Compounds of formula (II) may be prepared by reacting a compound of formula (VI)



(VI)

wherein R^{1a} is as defined for R^1 or an *N*-protecting group and R^2 , m and p are as defined above, with a compound of formula $A-S-L^3$ or $A-S-S-A$, wherein A is as defined above and L^3 is a leaving group such as halogen or methylsulfonyl. When Q represents a group of formula (i) or (ii) this reaction typically comprises the use of a base, for example in the case where X represents $-N=$, Y represents $-N(R^5)-$ and R^5 represents hydrogen, a metal hydride (eg. sodium hydride) in a suitable solvent such as *N,N*-dimethylformamide which is then allowed to react with the compound of formula $A-S-L^3$ or $A-S-S-A$.

Compounds of formula (VI) wherein Q represents a group of formula (i), X represents $-N=$, Y represents $-N(R^5)-$ and R^5 represents hydrogen may be prepared in accordance with the following process:



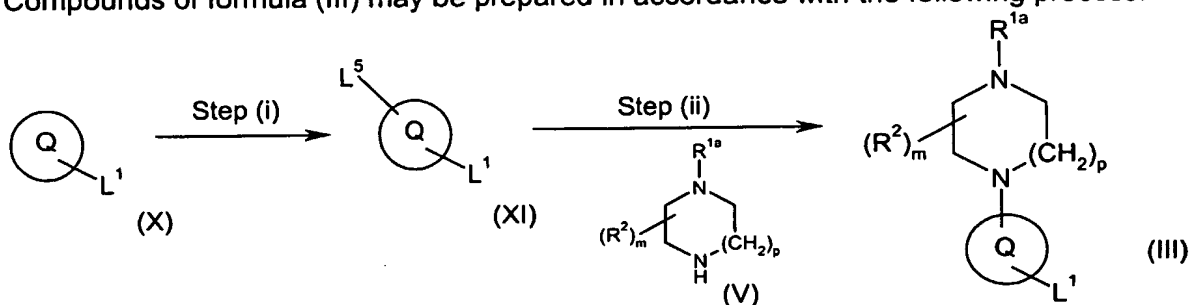
- 15 wherein R^{1a} is as defined for R^1 or an *N*-protecting group and R^2 , R^3 , R^{3a} , m , n and p are as defined above, L^4 represents a suitable leaving group such as halogen (eg. chlorine), Hal is a halogen atom such as chlorine or bromine.

Step (i) typically comprises the use of a base such as triethylamine or an excess of the compound of formula (V) and an inert solvent such as dichloromethane.

- 5 Step (ii) typically comprises the use of an inert solvent such as tetrahydrofuran at a suitable temperature (e.g. -40°C).

- Compounds of formula (VI) wherein Q represents a group of formula (ii), X represents N= , Y represents $\text{-N(R}^5\text{)-}$ and R^5 represents hydrogen may be prepared in an analogous manner to that described for the process above.
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Compounds of formula (III) may be prepared in accordance with the following process:

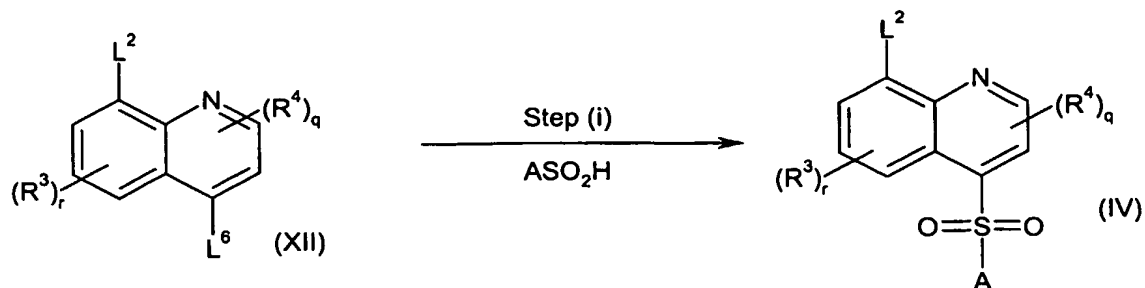


- 15 wherein R^{1a} is defined above for R^1 or an *N*-protecting group, R^2 , *m* and *p* are as defined above, Q represents a group of formula (iii) or (iv), L^1 represents a suitable leaving group, such as iodo or trifluoromethylsulfonyloxy and L^5 represents a suitable leaving group, such as chlorine.

- 20 Step (i) typically comprises reacting a compound of formula (X) with a suitable oxidant such as a peracid (e.g. 3-chloroperbenzoic acid or peracetic acid) in an inert solvent such as dichloromethane in order to generate the quinoline-*N*-oxide, followed by a combination of Lewis acid and nucleophile; for example this latter step may be advantageously carried out using phosphorus oxychloride.

- 25 Step (ii) typically comprises heating a mixture of compounds of formula (XI) and (V) in a suitable solvent such as ethanol, optionally in the presence of additional base (e.g. triethylamine or an excess of the compound of formula (V)).

- 30 Compounds of formula (IV) wherein Q represents a group of formula (iv) may be prepared in accordance with the following process:



wherein R^3 , R^4 , r , q , A and L^2 are as defined above and L^6 represents a suitable leaving group, such as halogen atom.

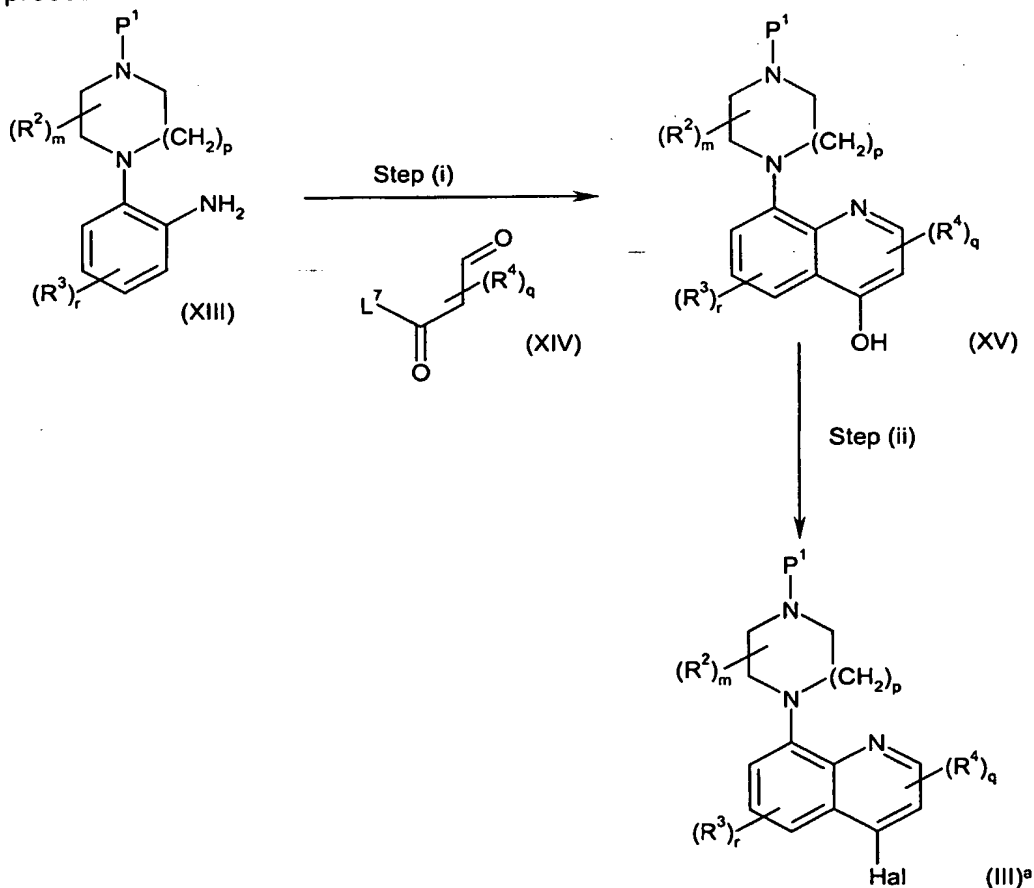
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Step (i) is typically carried out under basic conditions, for example using the sodium salt of the sulfinic acid compound in the presence of a suitable solvent, eg.

dimethylformamide. Alternatively this transformation may be carried out using a compound of formula $A-SH$ and subsequent oxidation in a manner similar to that

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described above for process (b).
Compounds of formula (III) wherein Q represents a group of formula (iv) and L^1 represents a halogen atom (Hal) may be prepared in accordance with the following process:



15

wherein R^2 , R^3 , R^4 , m, p, r and q are as defined above, L^7 represents a suitable leaving group, eg. an alkoxy group and P^1 represents a suitable protecting group, eg. trifluoroacetyl.

5

Step (i) typically comprises an initial condensation reaction under acidic conditions, followed by a thermal cyclisation of the resulting enamine in the presence of a suitably high boiling solvent, eg. diphenyl ether.

10 Step (ii) typically comprises the use of a suitable phosphorus halide or phosphoryl halide at an elevated temperature.

Compounds of formula (V), (VII), (IX), (X), (XII), (XIII) and (XIV) are known in the literature or can be prepared by analogous methods.

15

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

20 Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT₆ receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimer's disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from
25 drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia (in particular cognitive deficits of schizophrenia), stroke and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders
30 such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment
35 or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, obesity and cognitive memory disorders

The invention further provides a method of treatment or prophylaxis of the above
40 disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

5

5-HT₆ antagonists have the potential to be capable of increasing basal and learning-induced polysialylated neuron cell frequency in brain regions such as the rat medial temporal lobe and associated hippocampus, as described in International Patent Application No. PCT/EP03/00462. Thus, according to a further aspect of the present invention, we provide a method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

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Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

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Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

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For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for

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injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral
5 suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

10 The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will
15 vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

20 All publications, including but not limited to patents and patent applications, cited in this specification are hereby incorporated by reference as if each individual publication were individually indicated to be incorporated by reference herein as though fully set forth.

25 The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

30 4-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-3-nitropyridine (D1)

To a stirred suspension of 4-chloro-3-nitropyridine [Carceller *et al.*, *J. Med. Chem.* **1996** 39 487] (23.37 g, 0.147 mol) in dichloromethane (500 ml) under argon was added Et₃N (22.43 ml), followed by 1-Boc-piperazine (30.38 g, 0.14 mol). The reaction was left to stir for 72 h at room temperature. The solvent was then evaporated *in vacuo* and the
35 residues partitioned between dichloromethane (250 ml) and water (250 ml). The organic layer was then washed with 10% citric acid (250 ml), sat. NaHCO₃ (250 ml), brine (250 ml), dried (MgSO₄) and the solvents evaporated *in vacuo* to give the product as a dark yellow solid (D1) (45 g)

40 NMR (DMSO-d₆) : δ_H 1.42 (9H, s), 3.24-3.26 (4H, m), 3.46-3.47 (4H, m), 7.17-7.18 (1H, d), 8.38-8.39 (1H, d), 8.79 (1H, s)

Description 2

7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*]pyridine (D2)

To a solution of 4-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-3-nitropyridine (D1) (6.3 g, 20.5 mmol) in tetrahydrofuran (200 ml) at -50 °C under argon was added vinyl magnesium bromide (1M in THF; 67.4ml, 67.4 mmol) was added rapidly, keeping the temperature below - 40 °C. Reaction stirred at - 40 °C for 30 min, then poured into sat. NH₄Cl (1000 ml) and extracted with dichloromethane (2 x 500 ml). The combined organic layers were then dried (MgSO₄) and the solvent evaporated *in vacuo*. Purification by flash chromatography (MeOH / dichloromethane) gave the product as a brown solid (D2) (2.3 g).

NMR (CDCl₃) : δ_H 1.49 (9H, s), 3.35-3.39 (4H, m), 3.64-3.68 (4H, m), 6.59-6.61 (1H, d), 6.66-6.67 (1H, d), 7.39-7.41 (1H, d), 8.25-8.27 (1H, d), 11.45 (1H, br s)

Mass Spectrum: C₁₆H₂₂N₄O₂ requires 302; found: 303 (MH⁺)

Description 3**3-Phenylsulfanyl-7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*]pyridine (D3)**

Sodium hydride (60% in mineral oil, 39.7 mg, 0.99 mmol) was washed in hexane and then taken up in dimethylformamide (4 ml). 7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*]pyridine (D2) (200 mg, 0.66 mmol) was added and left to stir for 10min. Diphenyldisulfide (159 mg, 0.73 mmol) was added and the reaction left to stir for 16 h. The reaction mixture was then diluted with water (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water (50 ml), dried (MgSO₄) and the solvents evaporated *in vacuo*. Purification by flash chromatography (MeOH : DCM) gave the product as an off-white solid (D3) (115.3 mg).

NMR (CDCl₃) : δ_H 1.49 (9H, s), 3.35-3.39 (4H, m), 3.64-3.68 (4H, m), 6.58-6.61 (1H, d), 6.99-7.12 (5H, m), 7.63 (1H, s), 8.22-8.24 (1H, d), 12.45 (1H, br s).

Mass Spectrum: C₂₂H₂₆N₄O₂S requires 410; found: 411 (MH⁺)

Description 4**3-Phenylsulfonyl-7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*]pyridine (D4)**

To a stirred solution of 3-phenylsulfanyl-7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*]pyridine (D3) (50 mg, 0.12 mmol) in methanol (5 ml) was added potassium monopersulfate (150 mg, 0.24 mmol) in water (1 ml). The reaction mixture was stirred for 90 min and the solvents evaporated *in vacuo*. The residue was partitioned between dichloromethane (10 ml) and sat. NaHCO₃ solution (10 ml). The aqueous layer was re-extracted with dichloromethane and the combined organic extracts dried (MgSO₄) and the solvents evaporated *in vacuo* to give the product as a white solid (D4) (54.2 mg).

NMR (CDCl₃) : δ_H 1.47 (9H, s), 3.67-3.70 (4H, m), 3.90-4.30 (4H, br m), 6.46-6.48 (1H, d), 7.44-7.52 (3H, m), 7.85 (1H, br s), 7.95-8.00 (3H, m), 10.50 (1H, br s)

Mass Spectrum: C₂₂H₂₆N₄O₄S requires 442; found: 441 (M-H)

Descriptions 5 and 6

7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-4-methyl-3-phenylsulfonyl-4*H*-pyrrolo[3,2-*b*] pyridine (D5) and 7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1-methyl-3-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*] pyridine (D6)

- 5 To a stirred solution of 3-phenylsulfonyl-7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[3,2-*b*] pyridine (D4) (52.7 mg, 0.12 mmol) in ethanol (4 ml) was added potassium hydroxide (8.5 mg, 0.18 mmol). After 20min, the solvent was evaporated *in vacuo* and the residue re-dissolved in acetone (2 ml). Dimethyl sulfate (15 mg, 0.12 mmol) was then added and reaction stirred for 2 h. The reaction mixture was diluted with dichloromethane (10 ml) and washed with water (10 ml), dried (MgSO₄) and the solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc : dichloromethane) gave 7-(4-*tert*-butyloxycarbonyl) piperazin-1-yl-4-methyl-3-phenylsulfonyl-4*H*-pyrrolo[3,2-*b*] pyridine (D5) (8.8 mg) and 7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1-methyl-3-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*] pyridine (D6) (26 mg) as brown oils.

15 7-(4-*tert*-butyloxycarbonyl) piperazin-1-yl-4-methyl-3-phenylsulfonyl-4*H*-pyrrolo [3,2-*b*] pyridine (D5):

NMR (CDCl₃) : δ_H 1.49 (9H, s), 3.00 (4H, br s), 3.82 (4H, br s), 4.11 (3H,s), 6.28-6.30 (1H, d), 7.29 (1H, s), 7.44-7.51 (3H, m), 7.87-7.89 (2H, m), 8.17 (1H, s)

20 Mass Spectrum: C₂₃H₂₈N₄O₄S requires 456; found: 457 (MH⁺)

7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1-methyl-3-phenylsulfonyl-1*H*-pyrrolo [3,2-*b*] pyridine (D6):

25 NMR (CDCl₃) : δ_H 1.49 (9H, s), 3.00 (4H, br s), 3.50 (4H, br s), 4.11 (3H, s), 6.82-6.83 (1H, d), 7.44-7.51 (3H, m), 7.84 (1H, s), 8.27-8.29 (2H, m), 8.49-8.51 (1H, d)

Mass Spectrum: C₂₃H₂₈N₄O₄S requires 456; found 457 (MH⁺)

Description 7

2-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-3-nitro pyridine (D7)

- 30 To a stirred solution of 2-chloro-3-nitro pyridine (6.5 g, 0.041 mol) in dichloromethane was added 1-Boc-piperazine (8.0 g, 0.043 mol) and triethylamine (6.29 ml, 0.045 mol). The reaction was then stirred at room temperature, under argon for 3 h. The solvents were evaporated *in vacuo* and the residue partitioned between dichloromethane (150 ml) and water (100 ml). Aqueous layer was re-extracted with dichloromethane (2 x 150 ml) and the combined organic layers washed with 10% citric acid (100 ml), saturated aqueous NaHCO₃ (100 ml), water (100 ml), dried (Na₂SO₄) and the solvents evaporated *in vacuo* to give a yellow oil (D7) (12.1 g)

¹H NMR (CDCl₃) : δ 1.48 (9H, s), 3.40-3.50 (4H, m), 3.55-3.58 (4H, m), 6.78-6.81 (1H, m), 8.15 (1H, dd, J = 1.7, 8.0 Hz), 8.35 (1H, m)

40 Mass Spectrum: C₁₄H₂₀N₄O₄ requires 308; Found 209 ((M-Boc)H⁺)

Description 8

7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine (D8)

To a stirred solution of 2-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-3-nitro pyridine (D7) (1.0 g, 3.25 mmol) in THF at -50°C , under argon was added vinyl magnesium bromide (1.0 M in THF; 10.6 ml, 11.0 mmol) in one portion. Reaction was stirred at -40 to -45°C for 30 min before being quenched with sat. NH_4Cl solution. The mixture was extracted with dichloromethane (2 x 100 ml) and the combined organic layers dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give an orange oil. Purification by flash chromatography (dichloromethane / MeOH; 98:2 – 95:5), followed by re-purification (dichloromethane / EtOAc 95:5) gave the product as an orange solid (D8) (86 mg)

^1H NMR (CDCl_3) : δ 1.49 (9H, s), 3.35-3.40 (4H, m), 3.62-3.66 (4H, m), 6.54 (1H, dd, J = 2.0, 3.0 Hz), 7.22 (1H, d, J = 5.6 Hz), 7.28 (1H, dd, J = 2.8, 3.0 Hz) 7.92 (1H, d, J = 5.6 Hz), 8.45 (1H, br s)

Mass Spectrum: $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_2$ requires 302; Found 303 (MH^+)

Description 9**7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-3-phenylsulfanyl-1*H*-pyrrolo[2,3-*c*]pyridine (D9)**

Sodium hydride (60% in oil; 26 mg, 0.65 mmol) was washed with dry Et_2O and then dried under argon. This was then slurried in dry DMF (1 ml) and 7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine (D8) (130 mg, 0.43 mmol) in DMF (3 ml) was added, under argon. Reaction mixture was stirred at room temperature for 10 min, then diphenyldisulfide (133 mg, 0.47 mmol) was added and stirring continued at room temperature for 18 h. Reaction mixture was quenched with water (40 ml) and the mixture extracted with EtOAc (3 x 100 ml). Combined organic layers were washed with water, dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a red oil. Purification by flash chromatography (EtOAc / dichloromethane 20:80) gave the product as a pale red solid (D9) (85 mg)

NMR (CDCl_3) : δ_{H} 1.50 (9H, s), 3.39-3.43 (4H, m), 3.65-3.67 (4H, m), 7.08-7.10 (3H, m), 7.15-7.18 (3H, m), 7.53 (1H, d, J = 2.7 Hz) 7.95 (1H, d, J = 5.6 Hz), 8.55 (1H, br s)

Mass Spectrum: $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ requires 410; Found 411 (MH^+)

Description 10**7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-3-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridine (D10)**

To a stirred solution of 7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-3-phenyl sulfanyl-1*H*-pyrrolo[2,3-*c*] pyridine (D9) (57 mg, 0.139 mmol) in MeOH (5 ml) was added potassium monopersulfate (85 mg, 0.139 mmol) dissolved in water (1 ml). Reaction mixture was stirred at room temperature for 18 h before a further 1 eq. of potassium monopersulfate was added and reaction stirred for an additional 1 h. The solvents were evaporated *in vacuo* and the residue partitioned between dichloromethane and sat. NaHCO_3 solution. The aqueous layer re-extracted with dichloromethane (3 x 50 ml) and the combined organic layers washed with water (50 ml), dried (Na_2SO_4) and the solvents evaporated *in*

vacuo to give a brown solid. This material was then dissolved in triethylphosphite (3 ml) and heated at 130 °C for 3 h. After this period, reaction mixture cooled to room temperature and diluted with dichloromethane (50 ml), washed with water (2 x 50 ml) and the combined aqueous layers re-extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried (Na₂SO₄) and the solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc / dichloromethane 2:98 – 20:80) gave the product as a white solid (D10) (55 mg)

NMR (CDCl₃) : δ_H 1.49 (9H, s), 3.33-3.36 (4H, m), 3.61-3.63 (4H, m), 7.46-7.51 (4H, m), 7.93 (1H, d, *J* = 3 Hz), 8.01-8.05 (3H, m), 8.85 (1H, br s)

Mass Spectrum: C₂₂H₂₆N₄O₄S requires 442; Found 443 (MH⁺)

Description 11

7-Iodo-2-methylquinoline (D11)

Crotonaldehyde (4.96 ml, 60.0 mmol) was added dropwise over 1 h, *via* syringe pump, to a solution of 3-iodoaniline (12.5 g, 57.0 mmol) in 5M HCl (30 ml) at 90 °C. The reaction mixture was then heated at 100 °C for 3 h, before being cooled to room temperature and washed with Et₂O. To the aqueous solution was then added approx. 1 eq. of zinc (II) chloride, with vigorous stirring. The solution was then cooled to 0 °C and stirred for 45 min. The solid material was filtered off and washed (x 2) with cold 5M HCl. The crude product was dried on a filter paper and then stirred as a suspension in 2-propanol. The zinc chloride salt was filtered, dried and then re-suspended in water. The stirred mixture was treated with conc. ammonium hydroxide and the resultant slurry extracted with EtOAc. The combined organic layers were dried (Na₂SO₄) and the solvents evaporated *in vacuo* to give the free base as a dark green oil. This material was then dissolved in MeOH and 1.1 eq. of 1M HCl in Et₂O added. The solvents were then evaporated *in vacuo* to give a dark green solid. Re-crystallisation from MeOH gave the hydrochloride salt as a green solid. The free base was regenerated by stirring a suspension of the salt in saturated aqueous NaHCO₃ and extraction with dichloromethane to give the title compound (D11) (3.05 g).

NMR (CDCl₃) : δ_H 2.74 (3H, s), 7.30 (1H, d, *J* = 8.4 Hz), 7.49 (1H, d, *J* = 8.5 Hz), 7.74 (1H, dd, *J* = 1.6, 8.5 Hz), 8.00 (1H, d, *J* = 8.4 Hz), 8.46 (1H, s)

Mass Spectrum : C₁₀H₈IN requires 269; found: 270 (MH⁺).

Description 12

4-Chloro-7-iodo-2-methylquinoline (D12)

To a solution of 7-iodo-2-methylquinoline (D11) (1.6 g, 5.95 mmol) in chloroform (30 ml) was added 3-chloroperbenzoic acid (~ 50 %, 2.46 g, 7.14 mmol) in one portion. The reaction mixture was stirred at room temperature for 1 h, diluted with dichloromethane (100 ml) and then washed with saturated aqueous NaHCO₃. The aqueous layer was re-extracted with dichloromethane and the combined organic layers dried (Na₂SO₄) and the solvents evaporated *in vacuo* to give 7-iodo-2-methylquinoline-*N*-oxide as an orange oil which was used without further purification. To a stirred solution of the 7-iodo-2-

methylquinoline-*N*-oxide (1.70 g, 5.96 mmol) in dichloromethane (50 ml) was added POCl₃ (0.61 ml, 6.56 mmol) at 0 °C, under argon. Reaction mixture was stirred at room temperature for 12 h before a further 1 eq. of POCl₃ was added. Reaction mixture was then heated at 50 °C for 1.5 h, a further 1 eq. of POCl₃ added and the reaction heated at 60 °C for 2 h. After this period, the reaction mixture was cooled to room temperature and poured into ice / water (300 ml), basified with 0.88 NH₃ and extracted with dichloromethane (3 x 100 ml). Combined organic layers were washed with water (100 ml), dried (Na₂SO₄) and solvents evaporated *in vacuo* to give a brown oil. Purification by flash chromatography (5% EtOAc in PE) gave the title compound as a yellow solid (D12) (485 mg).

NMR (CDCl₃) : δ_H 2.71 (3H, s), 7.40 (1H, s), 7.83 (1H, dd, *J* = 1.6, 8.8 Hz), 7.88 (1H, d, *J* = 8.8 Hz), 8.46 (1H, d, *J* = 1.6 Hz)

Mass Spectrum : C₁₀H₇^{35/37}ClIN requires 303 / 305; Found 304 / 306 (MH⁺)

Description 13

4-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-7-iodo-2-methylquinoline (D13)

A mixture of 4-chloro-7-iodo-2-methylquinoline (D12) (475 mg, 1.56 mmol) and 1-Boc-piperazine (348 mg, 1.88 mmol) in ethanol (2 ml) were heated at 130 °C for 4 h in a sealed vessel. The reaction mixture was then cooled, the solvent evaporated *in vacuo* and the residue partitioned between dichloromethane and saturated aqueous NaHCO₃. The aqueous layer was re-extracted with dichloromethane (x 2) and the combined organic layers dried (Na₂SO₄) and the solvent evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (EtOAc / PE) gave the title compound as a yellow solid (D13) (485 mg).

NMR (CDCl₃) : δ_H 1.50 (9H, s), 2.66 (3H, s), 3.12-3.14 (4H, m), 3.68-3.71 (4H, m), 6.74 (1H, s), 7.66-7.68 (2H, m), 8.40 (1H, d, *J* = 1.6 Hz)

Mass Spectrum : C₁₉H₂₄IN₃O₂ requires 453; Found 454 (MH⁺)

Description 14

4-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-2-methyl-7-phenylsulfonylquinoline (D14)

A mixture of 4-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-7-iodo-2-methylquinoline (D13) (100 mg, 0.22 mmol), phenylsulfinic acid sodium salt (132 mg, 0.66 mmol) and CuI (126 mg, 0.66 mmol) were stirred together under argon, excluding light for 20 min. DMF (5 ml) was then added and the reaction heated at 120 °C for 24 h. the reaction mixture was then cooled to room temperature and partitioned between water (60 ml) and dichloromethane (60 ml). Aqueous layer was re-extracted with dichloromethane and the combined organic layers washed with water, dried (Na₂SO₄) and the solvents evaporated *in vacuo* to give a yellow oil. Purification by flash chromatography (EtOAc / PE) gave the title compound as an off-white solid (D14) (65 mg)

NMR (CDCl₃) : δ_H 1.50 (9H, s), 2.69 (3H, s), 3.11-3.14 (4H, m), 3.68-3.71 (4H, m), 6.81 (1H, s), 7.48-7.56 (3H, m), 7.89 (1H, d, *J* = 8 Hz), 8.00-8.07 (3H, m), 8.59 (1H, d, *J* = 2 Hz)

Mass Spectrum : $C_{25}H_{29}N_3O_4S$ requires 467; Found 468 (MH^+)

Description 15

8-Iodo-4-phenylsulfonylquinoline (D15)

- 5 Phenylsulfinic acid sodium salt (621 mg, 2.7 mmol), dissolved in DMF (10 ml), was added to a stirred solution of 4-bromo-8-iodoquinoline (300 mg, 0.89 mmol) in DMF (10 ml) at room temperature under argon. Reaction then stirred at 100 °C for 16 h. Reaction mixture was then diluted with water (50 ml) and extracted with EtOAc (3 x 50 ml). Combined organic layers were washed with brine (50 ml), dried ($MgSO_4$) and the
- 10 solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc / hexane) gave the title product as a yellow solid (306 mg).
- 1H NMR ($CDCl_3$) : δ 7.32-7.39 (1H, t), 7.49-7.65 (3H, m), 7.96-8.00 (2H, m), 8.21-8.23 (1H, d), 8.40-8.44 (1H, dd), 8.67-8.71 (1H, dd), 9.19-9.21 (1H, d).
- MS : $C_{15}H_{10}INO_2$ requires 395; found 396 (MH^+)

Description 16

8-(4-*tert*-Butyloxycarbonyl-piperazin-1-yl)-4-phenylsulphonyl quinoline (D16)

- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (48 mg, 0.08 mmol), $Pd(OAc)_2$ (11.4 mg, 0.05 mmol) and Cs_2CO_3 (248 mg, 0.75 mmol) were combined in dioxane (5 ml)
- 20 under argon and sonicated for 45 min. 1-Boc piperazine (236 mg, 1.28 mmol) and 8-iodo-4-phenylsulfonylquinoline (D15) (200 mg, 0.51 mmol) were combined in dioxane (5 mL) and added to the resulting blood red solution. Reaction was then left to heat at 100 °C for 16 h. The solvent was then evaporated *in vacuo* and the residue partitioned between DCM (10 ml) and water (10 ml). The organic layer was removed and the aqueous layer re-extracted with DCM (10 ml). Combined organics were washed with sat. $NaHCO_3$ (20 ml), 10% citric acid solution (20 mL), brine (20 mL), dried ($MgSO_4$) and the
- 25 solvents evaporated *in vacuo*. Purification by Flash chromatography (EtOAc/hexane) gave the title product as a yellow oil (51.2 mg).
- 1H NMR ($CDCl_3$) : δ 1.49 (9H, s), 3.27-3.31 (4H, m), 3.71-3.75 (4H, m), 7.14-7.15 (1H, dd), 7.48-7.59 (4H, m), 7.96-7.99 (2H, m), 8.17-8.19 (1H, d), 8.22-8.25 (1H, dd), 9.07-9.09 (1H, d).
- 30 MS : $C_{24}H_{27}N_3SO_4$ requires 453; found 454 (MH^+)

Description 17

2-(4-Methylpiperazin-1-yl) nitrobenzene (D17)

- 1-Fluoro-nitrobenzene (17.7 ml, 0.168 mol), 1-methyl-piperazine (16 g, 0.16 mol) and K_2CO_3 (24.3 g, 0.176 mol) were combined in DMSO (140 ml) and heated to 140 °C for 16 h. The reaction mixture was then cooled and partitioned between water (300 ml) and EtOAc (300ml). The aqueous was re-extracted with EtOAc (300 ml) and the combined
- 40 organics washed with water (600 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo* to give the title product as a dark orange oil (35.35 g)

¹H NMR (CDCl₃) : δ 2.36 (3H, s), 2.56-2.62 (4H, m), 3.08-3.10 (4H, m), 7.02-7.05 (1H, t), 7.14-7.16 (1H, dd), 7.45-7.50 (1H, m), 7.74-7.77 (1H, dd)

Description 18

5 2-(4-Trifluoroacetyl-piperazin-1-yl) nitrobenzene (D18)

α-chloroethylchloroformate (7.7 ml) was added to a solution of 2-(4-Methyl piperazin-1-yl) nitrobenzene (D17) (10 g, 45.2 mmol) in DCM (150 ml) with rapid stirring.

Diisopropylethylamine (DIPEA) (12.4 ml) was then added and the solution refluxed for 1 h. The solvent was then evaporated *in vacuo* and the residue refluxed in MeOH (150 ml) for 1 h. The solvent was then evaporated *in vacuo*, and the residue taken up in DCM (150 ml), under argon. Solution then cooled in an ice-bath and 2,6-lutidine (12.2 ml) added. Trifluoroacetic anhydride (6 ml) in DCM (50 ml) was then added dropwise and the solution left to stir for 16 h. The solution was washed with 10% citric acid solution (2 x 200 ml), brine (200 ml), dried (MgSO₄) and solvents evaporated *in vacuo*. Purification by flash chromatography (EtOAc/hexane) gave the title product as an orange solid (3.48 g).

¹H NMR (CDCl₃) : δ 3.11-3.15 (4H, m), 3.77-3.79 (2H, m), 3.85-3.88 (2H, m), 7.17-7.21 (2H, m), 7.53-7.57 (1H, m), 7.82-7.84 (1H, dd)

MS : C₁₂H₁₂F₃N₃O₂ requires 303; found 304 (MH⁺)

Description 19

2-(4-Trifluoroacetyl-piperazin-1-yl) aniline (D19)

2-(4-trifluoroacetyl-piperazin-1-yl) nitrobenzene (D18) (2.54 g, 11 mmol) was dissolved in EtOH (150 ml) under argon and palladium on carbon (10%, 300 mg) was added. Reaction mixture was hydrogenated at 1 atm for 16 h. The solution was then filtered through celite and concentrated to yield the title product as an off-white solid (2.99 g).

¹H NMR (DMSO) : δ 2.84-2.88 (4H, bs), 3.34 (4H, bs), 5.11 (2H, bs), 6.54-6.58 (1H, m), 6.69-6.71 (1H, m), 6.82-6.92 (2H, m)

MS : C₁₂H₁₄F₃N₃O requires 273; Found 274 (MH⁺)

Description 20

3-{2-[4-Trifluoroacetyl-piperazin-1-yl]-phenylamino}-but-2-enoic acid ethyl ester (D20)

2-(4-trifluoroacetyl-piperazin-1-yl) aniline (D19) (0.77 g, 2.7 mmol), ethylacetoacetate (0.36 g, 2.7 mmol) and acetic acid (0.17 ml) were stirred in toluene (5 mL) and then refluxed in Dean-Stark apparatus. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (EtOAc/hexane) to yield the title product as a clear oil (0.12 g)

¹H NMR (CDCl₃) : δ 1.25-1.30 (3H, t), 2.12 (3H, s), 2.94-2.97 (4H, m), 3.80-3.82 (2H, m), 3.89-3.91 (2H, m), 4.13-4.18 (2H, q), 4.73 (1H, s), 6.99-7.14 (4H, m), 10.70 (1H, s)

MS : C₁₈H₂₂F₃N₃O₃ requires 385; Found 386 (MH⁺)

Description 21

1,4-Dihydro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-1H-quinoline-4-one (D21)
 (3-{2-[4-(Trifluoroacetyl)-piperazin-1-yl]-phenylamino}-but-2-enoic acid ethyl ester (D20)
 (117 mg, 0.30 mmol) was refluxed in diphenyl ether (1 ml) for 30 min. The solution was
 5 then eluted through a Sep-Pak column (EtOAc/hexane, then MeOH) to give the title
 product as a brown oil (84 mg).

¹H NMR (CDCl₃) : δ 2.44 (3H, s), 3.08 (4H, bs), 3.20 (1H, bs), 3.65 (1H, bs), 4.13 (1H,
 bs), 4.63 (1H, bs), 6.13-6.14 (1H, d), 7.24-7.31 (1H, m), 7.40-7.43 (1H, dd), 8.13-8.16
 (1H, dd), 9.08 (1H, bs)

10 MS : C₁₆H₁₆F₃N₃O₂ requires 339; Found 340 (MH⁺)

Description 22

4-Chloro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-quinoline (D22)

1,4-Dihydro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-1H-quinoline-4-one (D21) (84
 15 mg, 0.25 mmol) was refluxed in POCl₃ (2 ml) for 2 h. The solution was then diluted with
 water (5 ml) and basified with 2M NH₄OH. Reaction mixture was then extracted with
 DCM (2 x 10ml) and the combined organic layers washed with water (20 ml), dried
 (MgSO₄), and the solvent evaporated *in vacuo* to give the title product as a brown oil (88
 mg).

20 ¹H NMR (CDCl₃) : δ 2.73 (3H, s), 3.42-3.49 (4H, m), 3.93-3.97 (2H, m), 4.01-4.05 (2H,
 m), 7.13-7.14 (1H, d), 7.44 (1H, s), 7.45-7.52 (1H, t), 7.87-7.91 (1H, dd)

MS : C₁₇H₁₆F₃N₃O requires 357; Found 358 (MH⁺)

Description 23

25 **2-Methyl-4-phenylsulfonyl-8-(4-trifluoroacetyl-piperazin-1-yl) quinoline (D23)**

4-Chloro-2-methyl-8-(4-trifluoroacetyl-piperazin-1-yl)-quinoline (D22) (88 mg, 0.25 mmol)
 was dissolved in DMF (5 ml) under argon. Phenylsulfinate sodium salt in DMF (5 ml) was
 added and the solution heated to 100 °C for 16h. Reaction mixture was then diluted with
 water (10 ml) and extracted with EtOAc (2 x 10 ml). The combined organic layers were
 30 washed with brine (20 ml), dried (MgSO₄) and the solvents evaporated *in vacuo* to give
 the title product as a brown oil (106.2 mg).

¹H NMR (CDCl₃) : δ 2.86 (3H, s), 3.39-3.43 (4H, m), 3.91-3.93 (2H, m), 3.99-4.01 (2H,
 m), 7.11-7.13 (1H, d), 7.44-7.59 (4H, m), 7.95-7.96 (2H, d), 8.14 (1H, s), 8.20-8.22 (1H,
 dd)

35 MS : C₂₂H₂₀F₃N₃O₃S requires 463; Found 464 (MH⁺)

Example 1

4-(3-Phenylsulfonyl-1H-pyrrolo[3,2-b]pyridin-7-yl)-piperazine hydrochloride (E1)

3-Phenylsulfonyl-7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1H-pyrrolo[3,2-b] pyridine (D4)
 40 (51 mg, 0.12 mmol) was taken up in 4M HCl (5 ml) and heated to 60 °C for 60min. The
 solvent was evaporated *in vacuo* to give the product as a white solid (E1) (39.8 mg)

NMR (CD₃OD) : δ_H 3.48-3.53 (4H, m), 4.05-4.08 (4H, m), 7.18-7.20 (1H, d), 7.58-7.69 (3H, m), 8.12-8.15 (2H, m), 8.28-8.30 (1H, d), 8.47 (1H, s).

Mass Spectrum: C₁₇H₁₈N₄O₂S requires 342; found: 343 (MH⁺)

5 Example 2

4-Methyl-7-piperazin-1-yl-3-phenylsulfonyl-4H-pyrrolo[3,2-b] pyridine (E2)

7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-4-methyl-3-phenylsulfonyl-1H-pyrrolo [3,2-*b*] pyridine (D5) was taken up in 4M HCl (1 ml) and heated to 60 °C for 1 h. Solvents were evaporated *in vacuo* to yield a brown solid (E2) (6.9 mg)

10 NMR (CD₃OD) : δ_H 3.53-3.55 (4H, m), 4.01-4.04 (4H, m), 4.28 (3H, s), 7.18-7.20 (1H, d), 7.60-7.75 (3H, m), 7.98-8.00 (2H, d), 8.27-8.29 (1H, d), 8.46 (1H, s)

Mass Spectrum: C₁₈H₂₀N₄O₂S requires 356; found 357 (MH⁺)

Example 3

15 1-Methyl-7-piperazin-1-yl-3-phenylsulfonyl-1H-pyrrolo[3,2-*b*] pyridine (E3)

7-(4-*tert*-butyloxycarbonyl)piperazin-1-yl-1-methyl-3-phenylsulfonyl-1H-pyrrolo [3,2-*b*] pyridine (D6) (58.9 mg) was taken up in 4M HCl (6 ml) and heated to 60 °C for 60 min. Solvents evaporated *in vacuo* to yield an orange solid (E3) (50.2 mg)

20 NMR (CD₃OD) : δ_H 3.54 (4H, br s), 3.76 (4H, br s), 4.20 (3H, s), 7.44-7.46 (1H, d), 7.56-7.69 (3H, m), 8.11-8.14 (2H, d), 8.47-8.49 (1H, d), 8.60 (1H, s)

Mass Spectrum: C₁₈H₂₀N₄O₂S requires 356; found 357 (MH⁺)

The following Examples (E4-E5) were prepared using an analogous method to that used for Examples E1-E3.

25

Example 4

1-Methyl-7-piperazin-1-yl-3-(2-fluorophenyl)sulfonyl-1H-pyrrolo[3,2-*b*] pyridine (E4)

Mass Spectrum: C₁₈H₁₉FN₄O₂S requires 374; found 375 (MH⁺)

30 Example 5

4-Methyl-7-piperazin-1-yl-3-(2-fluorophenyl)sulfonyl-4H-pyrrolo[3,2-*b*] pyridine (E5)

Mass Spectrum: C₁₈H₁₉FN₄O₂S requires 374; found 375 (MH⁺)

Example 6

35 7-Piperazin-1-yl-3-phenylsulfonyl-1H-pyrrolo[2,3-*c*] pyridine hydrochloride (E6)

A solution of 7-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl-3-phenylsulfonyl-1H-pyrrolo[2,3-*c*] pyridine (D10) (55 mg, 0.124 mmol) in 4M HCl (3 ml) and 1,4-dioxane (3 ml) was heated at 60 °C for 1 h. After this period, reaction mixture was cooled and the solvents evaporated *in vacuo* to give the product as an off-white solid (E6) (54 mg)

40 NMR (DMSO-*d*₆) : δ_H 3.25-3.29 (4H, m), 3.64-3.68 (4H, m), 7.47 (1H, d, *J* = 5.9 Hz), 7.57-7.67 (3H, m), 7.89 (1H, d, *J* = 6 Hz), 8.00-8.02 (2H, m), 8.49 (1H, m) 9.17 (2H, br s)

Mass Spectrum: C₁₇H₁₈N₄O₂S requires 342; Found 343 (MH⁺)

The following compounds of Examples E7-E8 were prepared in an analogous manner to Example 6:

5 **Example 7**

3-(2-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-pyrrolo[2,3-c]pyridine hydrochloride (E7)

Mass Spectrum: $C_{17}H_{17}FN_4O_2S$ requires 360; Found 361 (MH^+)

10 **Example 8**

3-(3-Fluorophenyl)sulfonyl-7-piperazin-1-yl-1H-pyrrolo[2,3-c]pyridine hydrochloride (E8)

Mass Spectrum: $C_{17}H_{17}FN_4O_2S$ requires 360; Found 361 (MH^+)

15 **Example 9**

2-Methyl-4-piperazin-1-yl-7-phenylsulfonylquinoline hydrochloride (E9)

To a stirred solution of 4-(4-*tert*-butoxycarbonyl)piperazin-1-yl-2-methyl-7-phenylsulfonylquinoline (D14) (60 mg, 0.128 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (2 ml) dropwise. Reaction mixture was stirred for 1 h and solvents evaporated *in vacuo* and partitioned between dichloromethane and saturated aqueous K_2CO_3 . Aqueous layer was re-extracted with dichloromethane (x 2) and the combined organic layers dried (Na_2SO_4) and the solvents evaporated *in vacuo* to give a colourless oil. This material was dissolved in dichloromethane / MeOH and precipitated with 1.1 eq. of 1M HCl in Et_2O . The solvents were evaporated *in vacuo* to give the title compound as a pale yellow solid (E9) (45 mg)

25 NMR ($DMSO-d_6$) : δ_H 2.67 (3H, s), 3.30-3.60 (8H, br m), 7.22 (1H, s), 7.64-7.75 (4H, m), 7.89-7.91 (1H, d, $J = 8.6$ Hz), 8.05 (3H, d, $J = 7.5$ Hz), 8.25 (1H, d, $J = 8.7$ Hz), 9.45 (2H, br s)

Mass Spectrum : $C_{20}H_{21}N_3O_2S$ requires 353; Found 354 (MH^+)

30

Example 10

4-Phenylsulfonyl-8-piperazin-1-yl quinoline (E10)

8-(4-*tert*-Butyloxycarbonyl-piperazin-1-yl)-4-phenylsulphonyl quinoline (D16) (51.2 mg, 0.11 mmol) was stirred with 20 % trifluoroacetic acid in DCM (10ml) for 1h. Solvents were then evaporated *in vacuo* and the residue partitioned between DCM (10ml) and sat. $NaHCO_3$ (10 ml). Aqueous layer re-extracted and the combined organic layers washed with brine (10 ml), dried ($MgSO_4$) and the solvents evaporated *in vacuo*. Purification by sep-pak chromatography (MeOH / NH_3 / DCM) gave the title product as a yellow solid (25.7 mg).

40 1H NMR ($CDCl_3$) : δ 3.25-3.27 (4H, m), 3.38-3.40 (4H, m), 7.18-7.19 (1H, dd), 7.50-7.59 (4H, m), 7.97-7.99 (2H, dd), 8.18-8.19 (1H, d), 8.21-8.24 (1H, dd), 9.07-9.08 (1H, s)

MS : $C_{19}H_{27}N_3SO_4$ requires 353; found 354 (MH^+)

Example 11**4-Phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E11)**

4-Phenylsulfonyl-8-piperazin-1-yl-quinoline (E10) (25.7 mg, 0.75 mmol) was dissolved in DCM (5ml) and 1M HCl in ether (80 μ L, 0.80 mmol) was added. Solvent evaporated *in vacuo* to give the title product as an orange solid (26.9 mg).

^1H NMR : δ 3.73 (8H, bs), 7.55-7.75 (5H, m), 8.00-8.02 (2H, d), 8.38-8.39 (1H, d), 8.50-8.52 (1H, d), 9.35-9.35 (1H, d), 10.15 (2H, bs)

Example 12**2-Methyl -4-phenylsulfonyl-8-piperazin-1-yl-quinoline (E12)**

2-Methyl-4-phenylsulfonyl-8-(4-trifluoroacetyl-piperazin-1-yl) quinoline (D23) (106 mg, 0.23 mmol) was dissolved in MeOH (5 ml) and water (1.5 ml). K_2CO_3 was added and the solution stirred for 90 min. The solvent was evaporated *in vacuo* and the residue partitioned between DCM / MeOH (10 ml) and water (10 ml). The aqueous layer was re-extracted with DCM / MeOH (10 ml) and the combined organics washed with brine (20 ml), dried (MgSO_4) and the solvent evaporated *in vacuo* to give the title product as an orange oil (88 mg).

^1H NMR (CDCl_3) : δ 2.86 (3H, s), 3.17-3.20 (4H, m), 3.30-3.34 (4H, m), 7.11-7.14 (1H, dd), 7.40-7.57 (4H, m), 7.94-7.97 (2H, m), 8.10-8.13 (2H, m)

MS : $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ requires 367; Found 368 (M $^+$)

Example 13**2-Methyl-4-phenylsulfonyl-8-piperazin-1-yl-quinoline hydrochloride (E13)**

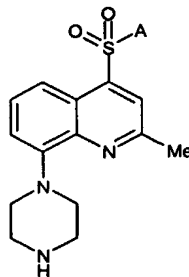
2-Methyl -4-phenylsulfonyl-8-piperazin-1-yl-quinoline (E12) (88 mg, 0.23 mmol) was taken up in DCM and 1M HCl in ether (0.274 ml) added. Solvents evaporated *in vacuo* to give the title product as a brown solid (93 mg).

^1H NMR (CDCl_3) : δ 3.06 (3H, s), 3.92 (8H, bs), 7.56-7.59 (2H, m), 7.64-7.73 (2H, m), 8.00-8.01 (2H, d), 8.24 (1H, bs), 8.28 (1H, s), 8.58-8.60 (1H, d), 10.35 (2H, bs)

MS : $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ requires 367; Found 368 (M $^+$)

Examples 14-16

Examples 14-16 were prepared in an analogous manner to Example 12



Example	A	MH ⁺	Formula
14	2-fluorophenyl	386	C ₂₀ H ₂₀ FN ₃ O ₂ S
15	3-fluorophenyl	386	C ₂₀ H ₂₀ FN ₃ O ₂ S
16	3-chlorophenyl	402	C ₂₀ H ₂₀ ClN ₃ O ₂ S

Pharmacological data

Compounds can be tested following the procedures outlined in WO98/27081.

- 5 The compounds of Examples E1-E16 were tested and showed good affinity for the 5-HT₆ receptor, having pKi values > 7.0 at human cloned 5-HT₆ receptors. In particular, Examples E6-E16 exhibited pKi values > 7.5 and Examples E9-E16 exhibited pKi values > 8.0.

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